PR001 gene therapy improved phenotypes in models of Parkinson’s disease with GBA1 mutation

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Background

Mutations in the GBA1 gene are believed to be the most common etiology of lysosomal storage diseases, with almost 300 mutations reported. GBA1 mutations cause Gaucher disease (GD), an autosomal recessive inherited disorder, and are a major risk factor for Parkinson’s disease. Deficiency in the GBA1 encoded enzyme glucocerebrosidase (GCase), a key lysosomal enzyme required for the normal metabolism of glycolipids, leads to the accumulation of the GCase glycolipid substrates glucosylsphingosine (GluSph) and glucosylceramide (GluCer) and ultimately results in toxicity and inflammation as seen in conditions such as Parkinson’s disease with GBA1 mutation (PD-GBA).

Gene therapy utilizes non-replicating viruses as shuttle vectors to deliver engineered DNA cargos to human cells. We have chosen adeno-associated virus (AAV)-based vectors as these have shown substantial promise in achieving stable, long-lasting transgene expression. Specifically, we have chosen AAV9 for our PD-GBA program as it is uniquely well-suited to deliver gene material to the brain, and has demonstrated efficacy, acceptable safety, and broad brain-wide biodistribution in third-party clinical trials in other disease areas. By expressing functional GBA1 in patients with PD-GBA, we aim to stop disease progression.

Approach

We have developed a gene therapy product candidate, PR001 (AAV9-GBA1). PR001 efficacy was evaluated in two mouse models: (i) a chemical model of GCase deficiency; (ii) a genetic model of PD-GBA. Both models exhibit pharmacological characteristics of PD-GBA, deficient GCase activity, accumulation of the glycolipid substrates of GCase, deficits in motor behavior, and neuroinflammatory changes including astrogliosis and microgliosis, reflecting neuroinflammation. PR001 efficacy and select safety endpoints were examined in these models, and further toxicology studies were performed in nonhuman primates.

CBE Model Establishment

- Conduritol-B-epoxide (CBE) is a pharmacological inhibitor of GCase
- Mice treated with CBE display phenotypes consistent with GCase loss-of-function
- A CBE dose-ranging study was performed to establish a CBE mouse model of PD-GBA
- Mice were dosed with daily intraperitoneal (IP) injections of phosphate buffered saline (PBS) or CBE (25 mg/kg, 37.5 mg/kg, 50 mg/kg) starting at postnatal day 8 (P8)
  • Animals were tissue collected on P27-29

Figure 1. CBE Model Validation

For all graphs: means are presented. Error bars are SEM. *p<0.05; **p<0.01; ***p<0.001.
- CBE treatment led to lethality, a gain in weight, and a motor coordination deficit in a dose-dependent manner
- All future CBE model studies used the 25 mg/kg dose as it recapitulated key features of PD-GBA

PR001 Efficacy in the CBE Model

- PR001 efficacy was examined in the CBE model
  • Animals were treated with PR001 or excipient at P3 via intracerebroventricular (ICV) injection
  • All comparisons were made to the CBE + Excipient group to examine model phenotypes and PR001 efficacy

Figure 2. PR001 treatment significantly improved body weight and motor deficits

Animals were weighted daily and subjected to motor behavioral tests prior to tissue collection on day 38-40. n=10 animals/group

PR001 Efficacy in the 4L/PS-NA Model

- PR001 efficacy was examined in the 4L/PS-NA model
  • This model harbors a pathogenic mutation in GBA1 (N394L) in addition to deficiency of the GCase activator saposin C, resulting in reduced GCase activity
  • Animals were treated with PR001 or excipient at 3-4 weeks of age via ICV injection
  • All comparisons were made to the 4L/PS-NA + Excipient group to examine model phenotypes and PR001 efficacy

Figure 6. PR001 treatment increased GCase activity and decreased lipid accumulation in the 4L/PS-NA model

Safety and Toxicology Studies

Safety was evaluated in each of these mouse models by H&E staining. The brain and peripheral tissues showed no adverse histopathologic findings or evidence of toxicity due to treatment. Biodistribution and toxicity studies were performed in nonhuman primates. Broad distribution of vector genomes throughout the CNS and periphery was observed. In-life assessments and H&E staining showed no adverse findings or evidence of toxicity due to treatment.

Conclusions

These studies demonstrate that PR001 effectively increased GCase expression, reduced glycolipid substrate accumulation, and reduced inflammation in mouse models of PD-GBA. In addition, PR001 treatment was well tolerated in the mouse models evaluated as well as in the NHP studies. Together, these studies support the clinical development of PR001 for the treatment of patients with PD-GBA.

References


Disclosures

All authors are or were employed by Prevail Therapeutics.